FERTILITY AND STERILITY®
VOL. 79, NO. 3, MARCH 2003

Published by Elsevier Science Inc.
Printed on acid-free paper in U.S.A.

Sex chromosome aberrations and transsexualism

Transsexualism is the most extreme form of gender dysphoria, which means that an individual with an apparently normal somatic sexual differentiation has the unalterable conviction that he or she is a member of the opposite sex. Hormonal treatment and sex reassignment surgery effectively enable transgender persons to make their bodies as congruent as possible with the preferred sex. The diagnosis is based on formal psychiatric classification criteria. However, the phenomenon remains enigmatic.

Chromosomal investigation of putative sex chromosome aberrations are routinely involved in the diagnostic management of transsexualism. Although this is more important for enabling diagnostic separation of transsexualism from, for example, genetically determined intersex, the discussion of to what extent other sex chromosome aberrations are involved in transsexualism comes up occasionally. Although different studies analyzing G-banded karyotypes have shown that most transsexuals have no microscopically detectable abnormalities, this discussion is reinitiated by a few reports describing male-to-female transsexuals with a 47,XYY karyotype. Recently, a female-to-male transsexual with a 47,XXX karyotype was reported (1).

In this study, we cytogenetically analyzed 30 male-to-female and 31 female-to-male transsexuals. They ranged in age from 19 to 63 years. In Austria, chromosomal investigation of putative sex chromosome aberrations is a required part of the routine diagnostic management of transsexualism. In addition, as part of genetic counseling, each patient was asked to sign a written informed consent concerning the other genetic analyses performed in the course of this study. This written informed consent was designed according to Austrian gene technology law. Chromosomes were prepared from peripheral lymphocytes, and G-banding was produced by means of the trypsin-Giemsa method. We could not detect any chromosomal aberrations with the exception of one balanced translocation 46,XY,t(6;17)(p21.3;q23). Importantly, no sex chromosomal aberrations, which would be detectable on the G-banded chromosome level, have been observed.

For a more detailed analysis of putative sex chromosome aberrations we performed fluorescence in situ hybridization (FISH) analyses using the locus-specific identifier DNA probes for the androgen receptor gene locus on chromosome Xq12 and for the SRY (sex-determining region of the Y chromosome) locus on chromosome Yp11.3 (Vysis, Inc., Downer's Grove, IL) according to the manufacturer's instructions. It is well known that aberrations of these regions can affect human sexual development. The aim of these FISH analyses was also to investigate putative submicroscopic alterations due to, for example, translocations involving sex chromosomes. This molecular-cytogenetic analysis did not reveal any submicroscopic aberrations in these regions: In all patients harboring a 46,XX karyotype we found two signals for the androgen receptor gene locus (on the two X chromosomes), but we did not find an additional signal on any other chromosome or an SRY-positive gene region. In all 46,XY transsexuals, we found one signal specific for the androgen receptor region and one SRY-specific signal on the X and the Y chromosome, respectively (Table 1). These data provide evidence that molecular-cytogenetic alterations affecting the androgen receptor gene region or the SRY region do not play a role in transsexualism.

Received April 4, 2002; revised and accepted July 19, 2002.

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0015-0282/03/$30.00
doi:10.1016/S0015-0282(02)04805-7

In addition to the testis determining factor (SRY), the Y chromosome harbors genes important for spermatogenesis. Microdeletions in the AZF region on the long arm of the Y chromosome can pathogenetically be involved in cases of male factor infertility associated with azoospermia or severe oligozoospermia. This region is divided into three nonoverlapping parts: AZFa, AZFb, and AZFc (the proximal part of the AZFc microdeletion is sometimes designated AZFd). The involvement of several different genes within these regions, such as DAZ, RBM, DFFRY, DBY, and CDY, has been described. Although all are candidate genes for the regulation of spermatogenesis, their real and full functional spectrum remains elusive. It is suggested that the expected frequency of AZF microdeletions in infertile men could be around 7%, varying between 1% and 55.5% (2, 3).

We performed AZF-specific polymerase chain reaction (PCR) analysis in the 30 male-to-female and 31 female-to-male transsexuals. Genomic DNA was prepared from peripheral lymphocytes by the proteinase K digest/protein-salting-out method. PCR analysis of the AZF region was performed using the Y chromosome deletion detection system from Promega (Madison, WI). This multiplex PCR system consists of 18 primer pairs that are homologous to previously identified and mapped sequence tagged sites to amplify nonpolymorphic short DNA regions within the AZF region. As negative and positive controls, every reaction included one sample of female and fertile male genomic DNA, respectively. In addition, control genomic DNA from patients known to harbor Y chromosome microdeletions were kindly provided by Prof. M. Simoni (Institute

TABLE 1

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	30 Male-to-female	31 Female-to-male
Karyotype	All normal 46,XY except one 46,XY,t(6;17)	All normal 46,XX
FISH for androgen receptor gene locus	All normal (one signal on the X chromosome)	All normal (two signals, each on one of the two X chromosomes)
FISH for sex-determining region Y	All normal (one signal on the Y chromosome)	All normal (no signal detected)
PCR for Y-chromosome microdeletions	29 normal; 1 deletion carrier	All normal (no positive PCR result for the AZF region)

Note: FISH = fluorescence in situ hybridization; PCR = polymerase chain reaction.

Hengstschläger. Genetics and transsexualism. Fertil Steril 2003.

of Reproductive Medicine of the University of Münster, Germany). In none of the patients with a 46,XX karyotype could we detect AZF gene sequences. These data once again provide evidence that none of them harbors Y chromosome material (translocated to another chromosome). Interestingly, one of the 30 male-to-female transsexuals exhibited an AZF microdeletion (Table 1).

The data described here provide evidence that genetic aberrations detectable on the chromosome level are not significantly associated with transsexualism. In addition, molecular-cytogenetic FISH analyses did not reveal deletions of the androgen receptor gene locus on chromosome Xq12 or of the SRY locus on chromosome Yp11.3. Multiplex PCR analyses demonstrated one AZF deletion in a male-to-female transsexual.

IVF techniques, such as intracytoplasmic sperm injection, enable treatment of impaired fertility associated with microdeletions of the Y chromosome. The couple should be informed about the risk that male children will inherit the defective Y chromosome from the father. The patients should further be informed that so far there is no known evidence of any other health consequences of these microdeletions. There is no doubt that the one case reported here of Y chromosome microdeletion associated with transsexualism should not be involved in up-to-date genetic counseling. It is further important that the description of a female-to-male transsexual with a 47,XXX karyotype (1) is not considered in the course of genetic counseling for a prenatal diagnosis of a 47,XXX karyotype.

However, the detection of one carrier of a Y chromosome microdeletion out of 30 male-to-female transsexuals could argue for further investigations. This is of special interest in light of the recent discussion of gamete banking before hormonal and sex reassignment surgery of transsexuals (4).

Acknowledgments: The authors thank M. Rosner, Prenatal Diagnosis and Therapy, and A. Maar, Obstetrics and Gynecology, for helpful discussion and technical support.

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